signaling may also regulate other cellular functions, including phagocytosis (15, 16). In future studies, it will be important to define which IGF-1–dependent cellular functions are modified by rhIGF-1 treatment. Because most preterm infants who develop BPD have been exposed to more than one inciting "injury," it would be useful to evaluate the efficacy of rhIGF-1 in "multihit" preclinical models of BPD (e.g., antenatal endotoxin followed by postnatal hyperoxia). Finally, because IGF-1 is a potent mitogen (17), longer-term preclinical and human studies are needed to examine its efficacy and safety in neonatal therapy. Nevertheless, the promising findings by Seedorf and colleagues lay the groundwork for future work evaluating rhIGF-1/BP3 as a possible therapeutic strategy for BPD. Of note, a phase 2 RCT (ClinicalTrials.gov Identifier: NCT03253263) evaluating the efficacy of rhIGF-1/BP-3 administration in preterm infants to prevent chronic lung disease through 12 months of corrected age (secondary outcome: BPD at 36 wk) is currently underway. Data from this trial should provide much-needed evidence regarding the usefulness of rhIGF-1/BP3 as a novel therapy to prevent and/or treat prematurity-associated lung disease. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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References

1. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723–1729.
2. Islam JY, Keller RL, Aschner JL, Hartert TV, Moore PE. Understanding the short- and long-term respiratory outcomes of prematurity and bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2015;192:134–156.
3. Jensen EA, Schmidt B. Epidemiology of bronchopulmonary dysplasia. *Birth Defects Res A Clin Mol Teratol* 2014;100:145–157.
4. Stiles AD, D'Ercole AJ. The insulin-like growth factors and the lung. *Am J Respir Cell Mol Biol* 1990;3:93–100.
5. Hellström A, Ley D, Hansen-Pupp I, Hallberg B, Löfqvist C, van Marter L, *et al*. Insulin-like growth factor 1 has multisystem effects on foetal and preterm infant development. *Acta Paediatr* 2016;105:576–586.
6. Lassarre C, Hardouin S, Daffos F, Forestier F, Frankenne F, Binoux M. Serum insulin-like growth factors and insulin-like growth factor binding proteins in the human fetus: relationships with growth in normal subjects and in subjects with intrauterine growth retardation. *Pediatr Res* 1991;29:219–225.
7. Bang P, Westgren M, Schwander J, Blum WF, Rosenfeld RG, Stangenberg M. Ontogeny of insulin-like growth factor-binding protein-1, -2, and -3: quantitative measurements by radioimmunoassay in human fetal serum. *Pediatr Res* 1994;36:528–536.
8. Epaud R, Aubey F, Xu J, Chaker Z, Clemessy M, Dautin A, *et al*. Knockout of insulin-like growth factor-1 receptor impairs distal lung morphogenesis. *PLoS One* 2012;7:e48071.
9. Han RN, Post M, Tanswell AK, Lye SJ. Insulin-like growth factor-I receptor-mediated vasculogenesis/angiogenesis in human lung development. *Am J Respir Cell Mol Biol* 2003;28:159–169.
10. Löfqvist C, Hellgren G, Niklasson A, Engström E, Ley D, Hansen-Pupp I; WINROP Consortium. Low postnatal serum IGF-I levels are associated with bronchopulmonary dysplasia (BPD). *Acta Paediatr* 2012;101:1211–1216.
11. Yılmaz C, Köksal N, Özkan H, Dorum BA, Bağcı O. Low serum IGF-1 and increased cytokine levels in tracheal aspirate samples are associated with bronchopulmonary dysplasia. *Turk J Pediatr* 2017;59:122–129.
12. Seedorf G, Kim C, Wallace B, Mandell EW, Nowlin T, Shepherd D, *et al*. rhIGF-1/BP3 preserves lung growth and prevents pulmonary hypertension in experimental bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2020;201:1120–1134.
13. Ley D, Hallberg B, Hansen-Pupp I, Dani C, Ramenghi LA, Marlow N, *et al*.; study team. rhIGF-1/rhIGFBP-3 in preterm infants: a phase 2 randomized controlled trial. *J Pediatr* 2019;206:56–65, e8.
14. Ma X, Bai Y. IGF-1 activates the P13K/AKT signaling pathway via upregulation of secretory clusterin. *Mol Med Rep* 2012;6:1433–1437.
15. Wang H, He J, Luo Y, Mu M, Guo S, Shen L, *et al*. IGF-1 promotes endocytosis of alveolar epithelial cells through PI3K signaling. *Ann Clin Lab Sci* 2019;49:3–8.
16. Xuan NT, Hoang NH, Nhung VP, Duong NT, Ha NH, Hai NV. Regulation of dendritic cell function by insulin/IGF-1/PI3K/Akt signaling through klotho expression. *J Recept Signal Transduct Res* 2017;37:297–303.
17. Wang YA, Sun Y, Palmer J, Solomides C, Huang LC, Shyr Y, *et al*. IGFBP3 modulates lung tumorigenesis and cell growth through IGF1 signaling. *Mol Cancer Res* 2017;15:896–904.

Treat the Symptom, Not the Cause? Pitolisant for Sleepiness in Obstructive Sleep Apnea

Pitolisant, an antagonist/inverse agonist of histamine H3 receptors, is a novel wake-promoting medication. It was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of sleepiness due to narcolepsy and has been available in the United States since November 2019. Because it is so new, and because it is a first-in-class drug, sleep medicine clinicians are early in the process of developing acumen about its applications (which patient, which dose, and when). Controlled clinical trials are very welcome in this regard.

In this issue of the *Journal*, Dauvilliers and colleagues (pp. 1135–1145) report data from a trial assessing the use of pitolisant for a non–FDA-approved indication, treatment of sleepiness in people with obstructive sleep apnea (OSA) who refuse first-line treatment with continuous positive airway pressure (CPAP) (1). This industry-sponsored trial randomized 268 people with OSA

Supported by the National Institute of Neurological Disorders and Stroke, NIH, under awards K23NS083748 and R01NS111280. The content is solely the responsibility of the author and does not necessarily represent the official views of the NIH.

Originally Published in Press as DOI: 10.1164/rccm.202001-0104ED on January 28, 2020

and an average apnea–hypopnea index (AHI) of 49, half of whom had comorbid cardiovascular disease, to pitolisant or placebo in a 3:1 ratio. This study has multiple strengths. It was rigorously designed, with central electronic randomization, matched pitolisant and placebo capsules, blinding of participants and outcome assessors, adequate power for the primary outcome, two independent statisticians, and a multisite design across 28 sites in 10 countries. Pitolisant was significantly better than placebo at reducing subjective sleepiness. It was also well tolerated, with similar rates of treatment-related adverse events observed for pitolisant and placebo, and only rare prolongation of QT intervals. Despite these strengths, the work by Dauvilliers and colleagues leaves several key unanswered questions for clinicians considering prescribing pitolisant.

First and foremost is the question of whether it is even appropriate to medicate OSA-induced sleepiness without treating the underlying OSA. OSA is a multisystem disease whose treatment may have health benefits beyond symptom control, in particular, reductions in blood pressure (2). As a result, the goal of OSA treatment is not only resolution of symptoms but also normalization of disease metrics such as the AHI (3). Although first-line CPAP is sometimes not tolerated, multiple other treatment options are recommended in clinical practice guidelines depending on the clinical situation, including mandibular advancement devices, surgical procedures in carefully selected patients, and weight loss (3–6). If sleepiness is improved by medication, it seems likely that people with OSA will have less motivation to pursue careful CPAP troubleshooting or effective CPAP alternatives, and the potential opportunity to improve their health will be lost. This is akin to treating insufficient sleep syndrome with a wake-promoting medication. The sleepiness and fatigue caused by insufficient sleep could be improved with wake-promoting medications, but the other physiologic benefits of sleep would be lost. Extending sleep durations can be very challenging because of family, work, and social obligations, but the benefits of sleep are worth this hard work. Similarly, however safe pitolisant may be, it is unlikely to be healthier than restoring normal breathing during sleep.

There is also a question regarding the clinical importance of this statistically significant benefit. Despite widespread use of the Epworth Sleepiness Scale (ESS) in clinical trials and clinical practice, there is still uncertainty about how much the ESS scores must change to represent a meaningful improvement. Dauvilliers and colleagues prespecified a minimal important difference of 3 points (1). The observed benefit of pitolisant was a modest 2.8 points and thus did not meet this threshold, raising the possibility that the average benefit of pitolisant for OSA is not meaningful. However, it can be challenging to determine minimal important differences (7), and other work has suggested that the minimal important difference in ESS for patients with OSA falls between 2 and 3 points (7, 8). Studies assessing other pharmacologic treatments of OSA sleepiness have shown similar reductions in ESS compared with placebo (1.7–4.5 points more than placebo with solriamfetol [9], 3.0 points more with modafinil [10], and 2.8 points more with armodafinil [10]), although some patients in these studies were also treated with CPAP, potentially creating a treatment ceiling effect. Supporting the argument that pitolisant's effect may be clinically significant, Dauvilliers and colleagues found improvements in several subjective secondary outcomes, including fatigue and patient and clinical global impressions.

What about objective measures of sleepiness? In Dauvilliers and colleagues' study, the Oxford Sleep Resistance Test was the only objective measure of sleepiness, and scores were not significantly improved with pitolisant (1). Similarly, objective cognitive performance was not improved. This differs from the use of pitolisant in narcolepsy, which was shown to result in a modest improvement of 1.5 minutes on the maintenance of wakefulness test (11). The absence of an objective benefit does not necessarily imply that pitolisant is ineffective for OSA sleepiness, because objective and subjective tests measure different aspects of the construct of sleepiness (12). However, objective tests such as the maintenance of wakefulness test may better predict important outcomes, such as driving safety (13). It is possible, but speculative, that sleepiness-related safety concerns may remain even after subjective sleepiness improves in patients with OSA treated with pitolisant, which would have important implications for decisions about whether or not to use this treatment strategy.

Finally, the maximum dose of pitolisant tested in Dauvilliers and colleagues' study was 20 mg, reached by approximately 85% of the participants (1). This is half the maximum dose tested in narcolepsy studies (11, 14) and lower than the maximum FDA-approved dose for narcolepsy of 35.6 mg. It is unclear whether higher doses might yield a more impressive benefit for sleepiness, and if so, at what cost of increased side effects.

Despite these remaining questions, in combination with prior work (11), this study by Dauvilliers and colleagues now establishes pitolisant as a treatment for sleepiness across at least three different pathophysiologic causes: hypocretin deficiency, OSA, and the as-yet-unidentified mechanism of narcolepsy type 2. Although this does not imply that it will be similarly effective for all causes of excessive daytime sleepiness, further studies of pitolisant are clearly warranted. This is particularly true for hypersomnolence disorders in which current treatment options are limited, such as idiopathic hypersomnia and hypersomnolence associated with medical or psychiatric disease, where preliminary clinical observations suggest that pitolisant can reduce sleepiness in people with idiopathic hypersomnia (15) or Prader-Willi syndrome (16). As such, this demonstration of a benefit from pitolisant for OSA-related sleepiness is an important step in the development of effective treatments across a wide range of sleepiness-producing disorders. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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References

1. Dauvilliers Y, Verbraecken J, Partinen M, Hedner J, Saaresranta T, Georgiev O, *et al.*; HAROSA II Study Group. Pitolisant for daytime sleepiness in patients with obstructive sleep apnea who refuse continuous positive airway pressure treatment: a randomized trial. *Am J Respir Crit Care Med* 2020;201:1135–1145.
2. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway

pressure: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med* 2019;15: 301–334.
3. Aurora RN, Casey KR, Kristo D, Auerbach S, Bista SR, Chowdhuri S, *et al*.; American Academy of Sleep Medicine. Practice parameters for the surgical modifications of the upper airway for obstructive sleep apnea in adults. *Sleep* 2010;33:1408–1413.
4. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med* 2019;15:335–343.
5. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, *et al*. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. *J Clin Sleep Med* 2015;11:773–827.
6. Hudgel DW, Patel SR, Ahasic AM, Bartlett SJ, Bessesen DH, Coaker MA, *et al*.; American Thoracic Society Assembly on Sleep and Respiratory Neurobiology. The role of weight management in the treatment of adult obstructive sleep apnea: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2018;198: e70–e87.
7. Patel S, Kon SSC, Nolan CM, Barker RE, Simonds AK, Morrell MJ, *et al*. The Epworth sleepiness scale: minimum clinically important difference in obstructive sleep apnea. *Am J Respir Crit Care Med* 2018;197: 961–963.
8. Crook S, Sievi NA, Bloch KE, Stradling JR, Frei A, Puhan MA, *et al*. Minimum important difference of the Epworth Sleepiness Scale in obstructive sleep apnoea: estimation from three randomised controlled trials. *Thorax* 2019;74:390–396.
9. Schweitzer PK, Rosenberg R, Zammit GK, Gotfried M, Chen D, Carter LP, *et al*.; TONES 3 Study Investigators. Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3): a randomized controlled trial. *Am J Respir Crit Care Med* 2019;199:1421–1431.
10. Kuan YC, Wu D, Huang KW, Chi NF, Hu CJ, Chung CC, *et al*. Effects of modafinil and armodafinil in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. *Clin Ther* 2016;38: 874–888.
11. Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, *et al*.; HARMONY I study group. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. *Lancet Neurol* 2013;12:1068–1075.
12. Sangal RB, Mitler MM, Sangal JM. Subjective sleepiness ratings (Epworth sleepiness scale) do not reflect the same parameter of sleepiness as objective sleepiness (maintenance of wakefulness test) in patients with narcolepsy. *Clin Neurophysiol* 1999;110: 2131–2135.
13. Philip P, Chaufton C, Taillard J, Sagaspe P, Léger D, Raimondi M, *et al*. Maintenance of wakefulness test scores and driving performance in sleep disorder patients and controls. *Int J Psychophysiol* 2013;89: 195–202.
14. Szakacs Z, Dauvilliers Y, Mikhaylov V, Poverennova I, Krylov S, Jankovic S, *et al*.; HARMONY-CTP study group. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2017;16: 200–207.
15. Leu-Semenescu S, Nittur N, Golmard JL, Arnulf I. Effects of pitolisant, a histamine H3 inverse agonist, in drug-resistant idiopathic and symptomatic hypersomnia: a chart review. *Sleep Med* 2014;15: 681–687.
16. Pullen LC, Picone M, Tan L, Johnston C, Stark H. Cognitive improvements in children with prader-willi syndrome following pitolisant treatment-patient reports. *J Pediatr Pharmacol Ther* 2019; 24:166–171.

Guidance on Statistical Reporting to Help Improve Your Chances of a Favorable Statistical Review

Over our tenure as the statistical editors of *AJRCCM* and *AnnalsATS*, we have observed recurrent methodological issues and reporting practices in submitted manuscripts that invariably lead to unfavorable reviews by statistical reviewers, content reviewers, and editorial board members. In an effort to help authors improve both the statistical rigor and clinical impact of their manuscripts, we have developed this document to both combine our suggestions and centralize resources and references that authors can use to avoid common pitfalls and improve reporting quality.

Clearly State the Aims of the Study in the Introduction

To assess whether the selected methods are appropriate for a study, the goals and specific hypotheses being tested must be clearly stated. This is often not the case. We recommend that authors use a PICO (population, intervention, comparator, outcome) (1) template or extension (2) (tailored PICO templates are available for most study designs) to develop clear study aims and research questions.

Follow Relevant Reporting Guidelines and Provide Details Regarding Analytic Decisions

Providing a full accounting of the study design, data collection, and data analysis can seem like an overwhelming task in any study, particularly within allowed word count limits. Thankfully, although a study *question* might be novel, the study *design* is usually not, and authors should take advantage of the many available guidelines and checklists that have been developed to detail what information should be reported for a given study design. To promote awareness, in Table 1, we list the guidelines for many common study designs, all of which are available from the EQUATOR (Enhancing the Quality and Transparency of Health Research) Network (www.equator-network.org/). The easiest way for authors to enhance the quality of their manuscript is to include all of the items and elements listed in the appropriate reporting guideline and accompanying checklist for their specific study design. These guidelines also provide a natural structure and sequence for authors to follow when writing their manuscript, because reporting elements are usually separated by each section of a manuscript

Supported by NIH/NHLBI grants K99 HL141678 and R00 HL141678 (M.O.H.).

Originally Published in Press as DOI: 10.1164/rccm.202003-0477ED on March 17, 2020